

### REMARKS

In the Office Action, the Examiner indicated that Applicants were required to submit a substitute specification showing the incorporated amendments and corrections from the preliminary amendments. Accordingly, a Substitute Specification accompanies this response, and incorporates all the changes in the preliminary amendments, as required.

#### Corrections to Specification

In regard to the correction at page 59, line 19 to page 60, line 13 of the Specification, Applicants point out that the context of page 59, line 19 to page 60, line 13 makes it clear to one of skill in the art that the transmembrane region, which contains 20 amino acids and is adjacent to the intracellular C terminus [amino acids (AA) 435-459], would end at AA 434 and begin at AA 415. Since the extracellular N terminus has 377 amino acids and begins at AA 38, i.e., just after the signal peptide (AA 1-37) it would end at AA 414. Thus, the error in the transmembrane AA numbering is apparent from that context.

## Corrections to SEQUENCE LISTING

### SEQ ID NO: 28

The corrections to SEQ ID NO: 28 in the SEQUENCE LISTING are necessary to correct the length and description of that sequence. As explained in the Specification at page 50, line 12 to page 51, line 3 under the heading Mapping of MN Gene Transcription Initiation Site, the MN gene has multiple transcription initiation sites. A transcription initiation site had been determined by rapid amplification of cDNA ends (RACE) to be at nucleotide (nt) 3537 of the genomic sequence shown in Figure 15, and then another site was determined by RNase protection assay to be at nt 3507. See the single-asterisked footnote in Table 1 on page 49 which indicates that the genomic position for the first exon "corresponds to transcription initiation site determined by RNase protection assay." [Specification, page 49, lines 27-31.] Therefore, the correct transcription initiation position in Table 1 is at position 3507 as determined by RNase protection assay.

### SEQ ID NO: 52

The corrections to SEQ ID NO: 52 in the SEQUENCE LISTING are made so that the SEQUENCE LISTING will comply with the corrections to the Specification made above at page 59, line

19 to page 60, line 13 which corrects the description of SEQ ID NO: 52.

Also enclosed is a substitute paper copy of the SEQUENCE LISTING and substitute computer readable copy (CRF).

Status of the Claims:

Claims 38-47 have been cancelled without prejudice. Applicants respectfully request the reinstatement of nonelected Claims 48-67, and the addition of new Claims 68-69, to point out with more particularity and clarity the subject matter regarded by the Applicants as their invention. Claims 48 and 53 have been amended to correct typographical/proofreading errors. The reinstated claims 48-67 are the same claims that were withdrawn from consideration as directed to a nonelected invention. Applicants respectfully request entry and consideration of the reinstated claims. Applicants respectfully request that the Examiner treat the reinstated claims as the elected claims.

Applicants respectfully submit that the reinstated claims 38-67 are supported throughout the application, as detailed in the Preliminary Amendment and Request for Declaration of an Interference with U.S. Patent No. 6,087,098 (pages 13-32), dated July 11, 2001, and in Appendix 1 which accompanied the Preliminary Amendment.

New claims 68 and 69 reflect now cancelled claims 46 and 47. The support for claims 46 and 47 detailed in the Preliminary Amendment submitted to the PTO on July 11, 2001, is also support for new claims 68 and 69.

Applicants respectfully submit that no new matter has been entered by the replacement of claims 38-47 with reinstated claims 48-67 and new claims 68 and 69 that are the same as the now cancelled claims 46 and 47, respectively.

Rejection under 35 U.S.C. §112, 1st Paragraph

Claims 38-47 stand rejected under 35 U.S.C. § 112, first paragraph "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." [Office Action, page 3.]

As Applicants have cancelled Claims 38-47, Applicants respectfully point out that the rejection of those claims is now moot. However, Applicants wish to point out that rejected claims 38-47, which were substantially based on claims 1-6 of the McKiernan et al. '098 patent to provoke an interference, have been cancelled for the reason that claims 1-6 of the McKiernan et al. '098 patent were not enabled and do not have

the cited utility. The McKiernan et al. '098 patent describes the use of a RT-PCR assay of MN mRNA, isolated from a blood sample of a subject, to diagnose clear cell renal carcinoma. However, preneoplastic and/or neoplastic tumor cells overexpressing MN mRNA, overexpress the same MN mRNA whatever the cell type of the tumor source. Therefore, it would not be possible for one of skill in the art to differentiate a diagnosis for clear cell renal carcinoma from any other possible tumor associated with abnormal MN gene overexpression, based only on MN mRNA found in blood.

The Office Action states on page 3, that "applicant has disclosed that an increase in MN protein is diagnostic of neoplastic and/or preneoplastic diseases and gives numerous examples including renal carcinoma, however, there is not explicit elaboration of the claimed RT-PCR process to diagnose renal carcinoma." The reason that there is no "explicit elaboration of the claimed RT-PCR process to diagnose renal carcinoma" is that there is no enablement for a specific diagnosis for renal carcinoma, based on RT-PCR of MN mRNA alone.

It was known to those of skill in the art at the time of filing of the McKiernan et al. '098 patent that the RT-PCR assay was useful for diagnosis only in the case of tissue-specific gene expression. For example, Smith et al. [Lancet 338:1227-1229 (1991)] have described the detection of melanoma

cells in peripheral blood using an RT-PCR assay for tyrosinase, a tissue-specific gene expressed in melanocytes, stating:

This method does not depend on the characterisation of cancer-specific genetic abnormalities and can be applied to any cancer for which tissue-specific genes can be identified, including epithelial cancers. It could prove useful in the diagnosis of primary or metastatic cancers, in assessing prognosis, and in detecting residue disease after treatment."

[Page 1227; emphasis added.]

In 1995, Burchill et al. described detection of epithelial cancer cells in peripheral blood by RT-PCR. This was possible because of the presence in the cancer cells of CK20, a cytokeratin gene which was not transcribed in normal hematopoietic cells: "We have found that reverse transcriptase (RT) PCR for tissue-specific gene expression is a useful technique for identifying small numbers of circulating cells in melanoma and neuroblastoma patients....The success of this technique is dependent on the availability of a specific target which can distinguish tumour cells from haematopoietic cells." [Br. J. Cancer 71: 278-281 (1995); emphasis added.] Therefore, it is necessary for the mRNA isolated from a blood sample to be tissue-specific, for the subsequent RT-PCR assay to be diagnostic for a specific type of cancer.

Originally, McKiernan et al. had thought that the G250 antigen was specific to renal carcinoma, and had based the use of RT-PCR for kidney cancer diagnosis (the '098 patent) on that premise; but subsequently, it was found that the G250 antigen was the same as the MN antigen, which is expressed by most tumor types. Applicants respectfully submit that RT-PCR detection of MN mRNA extracted from blood can be used to screen for the presence of preneoplastic/neoplastic disease, but not to diagnose a specific type of preneoplastic/neoplastic disease.

McKiernan et al., Cancer Res., 57: 2362-2365 (June 15, 1997), which contains much of the disclosure in the '098 patent reads at page 2364 (second column, bottom §):

"Unfortunately, there is no well-established renal carcinoma-specific marker available at this time." In contrast, the '098 patent makes the altered statement in the same context at column 12, lines 57-58: "Until now, there was no acceptable renal carcinoma specific marker available." Since the MN antigen, also known as CA IX or as G250, is not a renal carcinoma specific antigen, in that it is expressed in a myriad of other precancers/cancers, Applicants respectfully submit that the sentence in the '098 patent contradicting the McKiernan et al., Cancer Res. article is wrong, and that the RT-PCR assay described in the '098 patent is not diagnostic for renal cell

carcinoma, and certainly not diagnostic for clear cell renal carcinoma.

Applicants respectfully submit that the '098 patent claims are not enabled for diagnosing clear cell renal carcinoma and do not have that utility in view of the lack of a clear cell renal carcinoma specific marker. There is no suggestion nor enablement in the '098 patent for using a renal cell specific marker, as for example, (among other possible methods known to those of skill in the art) a monoclonal antibody specific to an antigen on the surface of renal cells but not on the cells of other tissues to isolate renal cells from a patient's blood. Then, the mRNA from said isolated renal cells could be extracted and amplified to see if the MN/CA 9 gene is being expressed as a diagnostic for renal cell carcinoma, that is, if there were such a renal cell specific antigen to which a monoclonal antibody were specific.

A RT-PCR method will work to screen for preneoplastic/neoplastic diseases expressing MN/CA IX, but can only be diagnostic for a specific preneoplastic/ neoplastic disease if a marker for the specific tissue involved is known. Such a MN/CA 9 RT-PCR method can be used in combination with most any tissue-specific marker to diagnose a specific preneoplastic/neoplastic disease. However, since, at least at the time of filing the application that was issued as the '098



patent, it appears that no such marker was known for either renal cells or renal cell carcinoma, and certainly not for clear cell renal carcinoma, the claims of the '098 patent are not enabled and have no utility.

Therefore, Applicants have respectfully requested cancellation of the claims 38-47, which were substantially modeled on the nonenabled claims 1-6 of the '098 patent, and the reinstatement of the nonelected claims 48-67 and new claims 68 and 69, based on the now cancelled claims 46 and 47.

#### Written Description Requirement for Claims 48-69

In rejecting Claims 38-47 under 35 U.S.C. § 112, first paragraph, the Office Action states on page 3, that "there is not explicit elaboration of the claimed RT-PCR process to diagnose renal carcinoma." Although the rejection of claims 38-47 is now moot in view of the cancellation of those claims, Applicants wish to respectfully submit that reinstated claims 48-67 and new claims 68 and 69, directed to the use of RT-PCR to screen for preneoplastic/neoplastic diseases meet the written description requirement. Support for this assertion has been previously provided in the Preliminary Amendment and Request for Declaration of an Interference with U.S. Patent No. 6,087,098 (pages 13-32), dated July 11, 2001, and in the accompanying Appendix 1.

For example, the Zavada et al. '676 patent (filed October 21, 1992) states (at column 2, lines 20-36):

This invention is directed to said MN gene, fragments thereof and the related cDNA which are useful, for example, as follows: 1) to produce MN proteins/polypeptides by biochemical engineering; 2) to prepare nucleic acid probes to test for the presence of the MN gene in cells of a subject; 3) to prepare appropriate polymerase chain reaction (PCR) primers for use, for example, in PCR-based assays or to produce nucleic acid probes; 4) to identify MN proteins and polypeptides as well as homologs or near homologs thereto; 5) to identify various mRNAs transcribed from MN genes in various tissues and cell lines, preferably human; and 6) to identify mutations in MN genes. The invention further concerns purified and isolated DNA molecules comprising the MN gene or fragments, thereof, or the related cDNA or fragments thereof.

[Emphasis added.]

As detailed in the Preliminary Amendment submitted on July 11, 2001 to the PTO, MN mRNA can be detected in "tissue specimens including smears, body fluids and tissue and cell extracts." [Zavada et al. '370 patent at col. 33, lines 51-57.]

One skilled in the art would recognize that the claimed steps incorporating a RT-PCR process are encompassed by the invention, because the specification states that the "invention is directed to said MN gene, fragments thereof and the related cDNA which are useful . . . to prepare nucleic acid

probes to test for the presence of the MN gene in cells of a subject; 3) to prepare appropriate polymerase chain reaction (PCR) primers for use, for example, in PCR-based assays ," in view of the fact that the use of RT-PCR techniques was conventional in 1992. See, for example, Kawasaki, E.S., PCR Protocols: A Guide to Methods and Applications (eds. Innis, M.A. et al.) Academic Press, San Diego, CA (1990), describing the steps to perform RT-PCR: "the RNA-PCR technique is a powerful new method for the analysis of RNA transcripts. Experiments that were previously extremely difficult or even impossible, such as mRNA quantitation from single cells, can now be easily performed by this modified PCR procedure." (See Kawasaki, page 27, last paragraph.) Applicants respectfully point out that one skilled in the art at the time the invention was made would understand the invention to encompass RT-PCR, given the disclosure of the sequence of the MN gene and its use in PCR and other nucleic acid based assays to detect preneoplastic/neoplastic diseases, along with Applicants' statements that the invention encompassed the MN mRNA and related cDNA.

Applicants further respectfully point out in regard to the written description requirement that a "specification is directed to those skilled in the art and need not teach or point out in detail that which is well-known in the art." [In re Myers, 671 USPQ 668, 671 (CCPA 1969)]. Moreover, "A patent need

not teach, and preferably omits, what is well known in the art."

[Spectra-Physics, Inc. v. Coherent, Inc., 3 USPQ 2<sup>nd</sup> 1737, 1743 (Fed. Cir. 1987); emphasis added.] As the Examiner pointed out in citing Fujikawa v. Wattansasin, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996), if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process, there is a lack of written description. [See Office Action page 5.] In that case, the "laundry list" disclosure in the specification did not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species. The facts of the instant application however are quite different. There is no laundry list, there are no undescribed species. There is only Applicants' disclosure of the sequence for the MN gene, along with related sequences such as the mRNA and cDNA sequences, and the teaching that use of the sequences could lead to diagnostic and prognostic tests for neoplastic or preneoplastic diseases using nucleic acid based assays, among others, including PCR. The instant specification would in fact reasonably and immediately lead one of skill in the art to envisage the claimed invention.

In Continental Can Co. USA v. Monsanto Co., 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) the court held that descriptive matter may be inherently present in a specification if one

skilled in the art would necessarily recognize such a disclosure. Further, the exact terms need not be used *in haec verba*, the specification must contain an equivalent description of the claimed subject matter. See Eiselstein v. Frank, 34 USPQ2d 1467, 1470 (Fed. Cir. 1995) ("[T]he prior application need not describe the claimed subject matter in exactly the same terms as used in the claims. . . .").

In Purdue Pharma L.P. v. Faulding Inc., 56 USPQ2d 1481, 1487 (Fed. Cir. 2000), applicants argued that a particular ratio of variables was described in the priority application, however, the court held that the specification did not disclose the subject matter as claimed. The instant application differs from the facts of Purdue in that one skilled in the art would have no difficulty in recognizing that the Applicants were in possession of the invention at the time the invention was made. Unlike Purdue, the method steps are not hidden within obscure characterizations of the features of the invention (a "substantially flat" serum concentration curve in the priority application vs. a "ratio of more than two" in the amended claims.)

In In re Alton, 37 USPQ2d 1578 (Fed. Cir. 1996), the Federal Circuit discussed the burden of establishing and overcoming a *prima facie* case of noncompliance with the written

description requirement during PTO prosecution of a patent application.

The examiner (or the Board, if the Board is the first body to raise a particular ground for rejection) "bears the initial burden . . . of presenting a prima facie case of unpatentability." . . . Insofar as the written description requirement is concerned, that burden is discharged by "presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims." . . . Thus, the burden placed on the examiner varies, depending upon what the applicant claims. If the applicant claims embodiments of the invention that are completely outside the scope of the specification, then the examiner or Board need only establish this fact to make out a prima facie case. . . . If, on the other hand, the specification contains a description of the claimed invention, albeit not in *ipsis verbis* (in the identical words), then the examiner or Board, in order to meet the burden of proof, must provide reasons why one of ordinary skill in the art would not consider the description sufficient.

[Emphasis added].

In the instant case, one skilled in the art would immediately envisage the claimed method steps from Applicants' disclosure. Therefore, Applicants respectfully submit that it would be understood by one skilled in the art at the time the application was filed that Applicants had possession of the pending claims.

Use of MN Detection as Method of Screening for  
Preneoplastic/Neoplastic Disease

The Examiner conceded on page 3, that "applicant has disclosed that an increase in MN protein is diagnostic of neoplastic and/or preneoplastic diseases and gives numerous examples. . . ."

The Zavada et al. '676 patent also describes PCR-based assays and the identification of MN mRNA transcribed from cells of various tissues and cell lines as aspects of this invention. At column 16, line 16 to column 17, line 29 the Zavada et al. '676 patent describes "Nucleic Acid Probes and Test Kits," and at column 17, lines 24-29 states:

Said probes thus can be useful diagnostically/prognostically. Said probes can be embodied in test kits, preferably with appropriate means to enable said probes when hybridized to an appropriate MN gene or MN mRNA target to be visualized. Such samples include tissue specimens, body fluids and tissue and cell extracts.

[Emphasis added.]

Applicants have informed those of skill in the art that they would be able to find MN mRNA in tissue specimens and body fluids, from which the mRNA could be extracted from preneoplastic/neoplastic cells therein. It would have been understood by one skilled in the art at the time the invention was filed that these mRNAs could be amplified and detected using RT-PCR techniques.

Claim Rejections under 35 U.S.C. § 102

Claims 38-47 stand rejected under 35 U.S.C.

§ 102(e), "as being anticipated by McKinernan (sic) et al. [U.S. Patent No. 6,087,098(2000)]." [Office Action, page 6.] The Office Action at page 6 states that "McKineran (sic) et al. teach an RT-PCR assay to detect renal carcinoma comprising all of the limitations 38-47," that "(a) generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus," and that "Claim 38 drawn to renal carcinoma is a generic claim. While that of McKinernan (sic) et al. is a species claim drawn to clear cell renal carcinoma."

Applicants have cancelled Claims 38-47, for the reasons detailed above that claims 1-6 of the McKiernan et al. '098 patent, on which now cancelled claims 38-47 were essentially modeled, were not enabled and without the cited utility [See Remarks under 35 U.S.C. § 112, 1st Paragraph Rejection section, supra]. Therefore the rejection of claims 38-47 is now moot.

However, Applicants respectfully point out that even if claims 38-47 had not been canceled, the McKiernan et al. '098 patent would not anticipate the claims because the McKiernan et al. '098 patent is not effective prior art. The McKiernan et al. '098 patent is not effective prior art for the reasons that the instant claims are entitled to an earlier priority date than



the McKiernan et al. '098 patent, and also for the reason that the disclosure of the McKiernan et al. '098 patent is not an enabling disclosure and that the claims do not possess the recited utility.

The instant application claims priority from the grandparent application, the Zavada et al. '676 patent (filed Oct. 21, 1992), and the parent to the instant application, the Zavada et al. '370 patent (filed June 7, 1995). In contrast, the McKiernan et al. '098 patent claims priority from April 15, 1997, almost five years later. Further, in the '676 and '370 patents, Applicants described the genus, the use of PCR to detect increased levels of MN mRNA as diagnostic/prognostic for preneoplastic/neoplastic diseases. The instant application is a continuation of the Zavada et al. '370 patent, and has the same specification. Therefore, the instant application is prior art to the McKiernan et al. '098 patent. Applicants respectfully submit that the McKiernan et al. claims 1-6 to the species concerning clear cell renal carcinoma would not anticipate the generic claims supported by the disclosures of the Zavada et al. '676 and '370 patents, even if the McKiernan Claims 1-6 were enabled and had the recited utility.

### Provisional Double Patenting Rejection

Claims 38-47 are provisionally rejected "under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1-10 of U.S. patent No. 6,027,887 in view of Samid [US Patent No.: 5,605,930 (1997)]."

[Office Action, page 7.] The Office Action further states at page 7:

Claims 1-10 of U.S. Patent No. 6,027,887 teach all of the limitations of Claims 38-47 except this patent's claims do not teach RT-PCR as recited in Claims 38-47, however, as RT-PCR and it (sic) use to detect abnormal gene expression, was well known at the time of the invention (07 JUN 95) as evidenced by Samid...it would have been, absent an unexpected result, *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method taught by Claims 1-10 of U.S. Patent No. 6,027,887 with the teachings of Samid.

Applicants respectfully traverse this rejection, and point out that the teachings of the instant application, and of the parent and grandparent applications from which it claims priority, encompass RT-PCR. Therefore, the instant claims cannot be rendered obvious by the disclosure of the priority application in view of Samid. The instant application is a continuation of the Zavada et al. '370 patent, in which Applicants described the use of PCR to detect increased levels of MN mRNA as diagnostic/prognostic for preneoplastic/neoplastic disease. If necessary, Applicants will submit a Terminal

Disclaimer upon allowance of claims 48-67 and new claims 68 and 69.

#### Request for a Declaration of Interference

The Examiner stated that when a party to an interference seeks the benefit of an earlier-filed U.S. patent application, the earlier application must meet the requirements of 35 USC 120 and 35 USC 112, first paragraph for the subject matter of the count, and that the earlier application must meet the enablement requirement and must contain a written description of the subject matter of the interference count. The Examiner cited Hyatt v. Boone, 47 USPQ2d 1128, 1130 (Fed. Cir. 1998) for the proposition that proof of a constructive reduction to practice requires sufficient disclosure under the "how to use" and "how to make" requirements of 35 USC 112, first paragraph, and Kawai v. Metlesics, 178 USPQ 158, 163 (CCPA 1973) for the proposition that a constructive reduction to practice is not proven unless the specification discloses a practical utility where one would not be obvious.

Applicants respectfully submit that the earlier filed U.S. patent application, now the Zavada '676 patent, does satisfy the "how to use" and "how to make" requirement of 35 USC § 112, first paragraph. Similarly, Applicants respectfully submit that the utility requirement is also met.

The Examiner also indicated at page 8 that the

written description must include all the limitations of the interference count, or the applicant must show that any absent text is necessarily comprehended in the description provided and would have been so understood at the time the patent application was filed. Furthermore, the written description must be sufficient, when the entire specification is considered, such that the 'necessary and only reasonable construction' that would be given it by a person skilled in the art is one that clearly supports each positive limitation in the count.

Applicants respectfully direct the Examiner's attention to the discussion above where the written description support for claims 48-69 is set forth.

As claims 38-47 have been cancelled, Applicants note that direct correspondence between claims 1-6 of the McKiernan et al. and the instant claims 48-69 is not longer met. However, pending claims 48-69 encompass the claim limitations of the McKiernan et al. patent and hence an interference is still proper.

Specifically, instant claim 48 is directed to

A method of screening for  
preneoplastic/neoplastic disease associated  
with abnormal MN gene expression comprising:

(a) determining whether abnormal MN  
gene expression is present in a vertebrate  
using a nucleic acid based assay on a sample  
from said vertebrate; and

(b) if abnormal MN gene expression is  
determined to be present in said vertebrate,

determining that said vertebrate has a significant risk of having preneoplastic/neoplastic disease;

wherein said MN gene encodes an MN protein that is encoded by a nucleic acid having a nucleotide sequence selected from the group consisting of:

(1) SEQ ID NO: 1;

(2) nucleotide sequences that hybridize under stringent conditions to complement of SEQ ID NO: 1; and

(3) nucleotide sequences that differ from SEQ ID NO: 1 or from the nucleotide sequences of (b) in codon sequence due to the degeneracy of the genetic code.

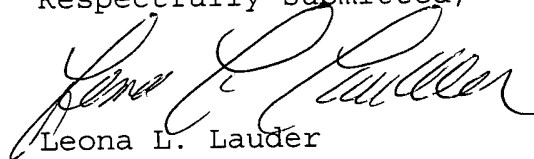
Claim 48 reads on McKiernan et al. claim 1 in that the method claimed in claim 48 would necessarily screen for the presence of clear cell renal carcinoma, as well as a myriad of other neoplastic and preneoplastic diseases, as set forth in the instant specification.

Similarly the other pending claims read on and encompass claims 2-6 of the McKiernan et al. patent. In view of the fact that the enablement, utility and written description requirements are met as discussed above, Applicants respectfully request that the Examiner declare an interference with claims 1-6 of the McKiernan et al. patent.

#### CONCLUSION

Applicants respectfully conclude that the claims as amended are in condition for allowance, and earnestly request that the claims be promptly allowed. If for any reason the Examiner feels that a telephone conference would expedite the prosecution of the instant application, the Examiner is invited to telephone the undersigned Attorney for the Applicants at 415-981-2034.

Respectfully submitted,

A handwritten signature in cursive script, appearing to read "Leona L. Lauder".

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Dated: